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Harmonising Adverse Drug Reaction Terminology

The Role of the Council for International Organizations of Medical Sciences

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Abstract

Health professionals from different countries are known to differ considerably in their use of medical terminology, including the terminology used for adverse drug reactions (ADRs) and in the exact meanings attributed to terms.

To remedy this situation, the Council for International Organizations of Medical Sciences (CIOMS) has attempted to provide definitions and basic requirements for proper use of ADR terms. The work has concentrated on terms liable to be misinterpreted and those used for serious and frequently reported ADRs. For every selected term a short monograph has been prepared. It consists of a preamble, definition, basic requirements for use of the term and additional comments, if any. In cooperation with medical experts, drug regulators and the pharmaceutical industry, 13 papers have been published so far. Approximately 160 terms have been defined and work on another 50 terms continues.

The full collection of monographs will eventually appear in the form of a book and CD-ROM intended to help doctors fill in case reports, and regulatory agencies and the pharmaceutical industry assess reports.

Pharmaceutical companies receive numerous reports of suspected ADRs from medical practitioners and other prescribing professionals. Each company is required to transmit these reports to the drug regulatory agency of the country, or countries, in which the drug is used. Therefore, in addition to receiving the correct name of the ADR, collecting and evaluating centres, regardless of whether they are part of a regulatory agency or a pharmaceutical company, need to be provided with sufficient supporting data to be convinced that what is reported was what was actually observed, and that the ADR term used represents the observed event.

The Council for International Organizations of Medical Sciences (CIOMS) is an international, nongovernmental, nonprofit organisation established in 1949 under the auspices of the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural Organization (UNESCO). It has its office in the premises of the WHO in Geneva. It acts as a sounding-board for informed opinion on new developments in biology and medicine. It also explores the social,

ethical, moral, administrative and legal implications of those developments. Since 1977 it has functioned as an independent forum for policy discussions between research-based pharmaceutical companies and national regulatory authorities.

The advent of international drug monitoring in the late 1960s (the WHO Pilot Research Project for International Drug Monitoring began its operations in 1968)[1] and the directions that drug monitoring took in the following years, has led to the creation of large databases of heterogeneous origins. This is true not only for data collected by international organisations such as WHO, but also for data collected by major pharmaceutical companies with worldwide activities.

Although most cases of suspected adverse drug reactions (ADRs) are reported by physicians trained (irrespective of country) in what is called 'western medicine', differences among countries in the use and interpretation of certain medical terms are quite large. Even within 1 country doctors differ in knowledge and type of experience, sometimes because physicians train in 1 country and practice in another. This may result in the use of different terms for the same event. The practicing physician is the main beneficiary of ADR data. However, physicians also generate most of the original observations and thus are largely responsible for the quality of ADR data received. In general, reported ADR data are incomplete and of poor quality.[2-5]

In 1986, CIOMS set up a Working Group on International Reporting of Adverse Drug Reactions to explore means of coordinating and standardising reporting of ADRs. The outcome was the introduction in 1990 of an international form based on agreed and tested procedures for reporting certain categories of ADRs – the so-called CIOMS form.[6] The success of this project led to the creation, always under the auspices of CIOMS, of subsequent working groups known as CIOMS II,[7] III,[8] IV and V. These have dealt with other matters relevant to drug safety. However, these working groups have not dealt with the important matter of definitions and basic requirements for proper use of ADR terms.

At a meeting organised by CIOMS in 1994, it was decided that the Medical Dictionary for Drug Regulatory Affairs (MedDRA)[9] would be the basis for further work in developing an international medical terminology for drug regulatory purposes. However, data entry from both the WHO Adverse Reaction Terminology (WHOART) and Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) would be included to facilitate transfer of historical data. It was also recommended that work on definitions of preferred terms, started by CIOMS, be continued, with the ultimate goal of establishing an unambiguous international medical terminology for regulatory affairs.

1. Standard Definitions and Basic Requirements for Proper Use of Terms

Health professionals from different countries are known to differ considerably in their use of medical terminology, including the terminology used for ADRs and in the exact meanings attributed to terms. For example, in some European countries, as opposed to the UK, the term 'thrombophlebitis' is used to describe a group of conditions, including deep venous thrombosis.

In some countries pharmaceutical companies receive numerous reports of suspected ADRs from medical practitioners and other prescribing professionals. Each company is required to transmit these reports to the drug regulatory agency of the country where the report originated. Moreover, in cases of particularly important or severe ADRs, companies are often also required to transmit the ADR reports to the regulatory authorities of other countries in which the suspected product is marketed.

The heterogeneity in reporting ADRs is sometimes due to different codes or abbreviations used, for example for a drug form, dosage regimen, or names of drugs. These can be streamlined with simple translating procedures built into computer programmes.

More difficult to handle internationally is information that requires more detailed medical knowl-

edge, i.e. reasons for taking a drug and ADRs suspected of being causally related to drug treatment. The International Classification of Diseases (ICD)[10] helps with reporting the reasons for taking a drug. However, from the point of view of drug safety, a correct diagnosis of the suspected ADR is of particular importance.

The need to establish requirements for the proper diagnosis of a suspected ADR and to describe it with the correct terms is particularly evident in the case of spontaneous monitoring of single case reports. This is for the following reasons.

- Single case reports still represent the most important type of information for raising suspicions, generating signals, and frequently, for taking action.
- Single case reports frequently lack details usually present in clinical studies.
- Single case reports are by definition a collection of suspicions concerning both the occurrence of the ADR and the causal relationship between the reaction and the treatment.
- Single case reports, as a rule, are transmitted by the reporting doctor to a collecting centre at either the drug regulatory agency or a pharmaceutical company and quite often between these organisations as well. They are thus assessed by people far removed from the patient.

It is understandable therefore that the collecting and evaluating centres, regardless of whether they are part of a regulatory agency or a pharmaceutical company, need to be provided with both the name of the ADR and sufficient supporting data to be convinced that what is reported was what was actually observed, and that the ADR term used represents the observed event. Such an evaluation is unrelated to the assessment of causality, which is a different problem and requires various kinds of additional information.

Contrary to spontaneous reporting, clinical studies are by design subject to much stricter protocols, validation procedures, etc., so that in most cases the desired details are already included.

In setting requirements for the proper use of ADR terms for spontaneous reporting, the level of detail that a case report should include in order to convince the evaluator that the reported reaction took place should be neither too high nor too low. If it were too high, too few cases would pass the requirements, thus seriously limiting the practical use of the whole effort. At the same time it must not be too low.

What should be considered is the elaboration of basic requirements at a level of sophistication that an average reporting physician can meet. In many instances it would probably be sufficient to transcribe certain details, normally recorded in patients' files, into the ADR report. For example in reporting 'hypertension', the physician has certainly taken the patient's blood pressure, but only rarely are the readings included in the case report. It should be noted that definitions and basic requirements for a given term will depend, to a certain extent, on the structure and level of detail of the ADR terminology for which they are prepared.

It is exactly the availability of such additional details that allows the evaluator, either with a regulatory agency or in the pharmaceutical industry, to accept this essential part of the case report, not on its face value, but in an informed way. Should such an approach be implemented, the resultant database of collected information would consist of 2 types of case reports: those that meet the basic requirements and those that do not meet them. Of course, no reported case would be discarded because of insufficient details.

The lack of universally standardised definitions of ADRs has been a daily problem for those concerned with drug safety. To describe an adverse event, doctors use terms derived from their medical education or their preconceptions of the mechanisms of reactions to drugs. The regulatory authority or the pharmaceutical firm records this information in the reporters' terms and other terms that the evaluator considers equivalent, chosen from an internationally agreed terminology. However, there are several international terminologies (the most important are WHOART, COSTART and the soon operational MedDRA) and they are difficult to compare since the terms they contain have not

been defined on either a scientific or a practical basis.

Medical dictionary or textbook definitions of ADRs are often contradictory and difficult to use in practice. However, an accurate term must be used for each ADR in order to record, report or list it, and to comply with regulatory requirements concerning its labelled or unlabelled nature or severity.

2. Method of Work

Because of the obvious interest of pharmaceutical companies in the proper assessment of their products and that of drug regulatory authorities in the proper assessment of case reports in general, the need arose to avoid misunderstandings and to streamline communication between all users of ADR data. In 1987 the first attempts to remedy this situation were initiated by the Roussel-Uclaf group.[11] The company organised a series of consensus meetings involving pharmacovigilance and clinical experts in France. The activities of CIOMS in the field of drug safety prompted the French group, already recognising the interest of internationalisation of this activity, to turn to it.

At about the same time, in 1990, at the request of a group of 7 German pharmaceutical companies, members of Verband Forschender Arzneimittelhersteller e.V. in Bonn, Germany (Bayer AG, Leverkusen; Boehringer Ingelheim GmbH, Ingelheim; Boehringer Mannheim GmbH, Mannheim; Hoechst AG, Frankfurt; Knoll AG, Ludvigshaven; E. Merck AG, Darmstadt; Schering AG, Berlin) and 3 Swiss companies associated with Interpharma, Basel [Ciba-Geigy AG, Basel; Sandoz AG, Basel (now Novartis AG); F. Hoffmann-La Roche AG, Basel], CIOMS initiated a project for defining certain ADR terms employed in spontaneous reporting of single cases of suspected ADRs, and for proposing basic requirements for their proper use. In 1996 this group was joined by Sanofi Pharma SA, Paris.

CIOMS has thus become the focus for an ongoing collaborative project involving national drug regulatory authorities, pharmaceutical manufacturers and representative bodies of medical specialties, aimed at updating classification, and providing definitions and basic requirements for proper use of ADR terms. In this way CIOMS is making an essential contribution to effective monitoring of ADRs.

The description that follows refers to the ongoing current procedure being used by CIOMS which is undergoing minor modification reflecting experiences gained so far. Doctors reporting ADRs use thousands of terms which in turn are reflected in ADR terminologies. It is neither possible nor necessary to define all those terms and to set criteria for their use. Thus, one of the first tasks has been to establish general criteria that would help in deciding which terms should be considered.

The following criteria have been established.

- Terms liable to be misinterpreted. Terms that tend to be misdiagnosed or terms that could be understood differently in different medical care or medical educational systems. This is the most essential criterion.
- Terms that designate serious ADRs. Serious ADRs are those that are fatal, life-threatening, cause hospitalisation, result in persistent or significant disability or incapacity, require intervention to prevent permanent damage or cause a congenital anomaly. These type of reactions certainly require a high degree of certainty that what was reported really did occur.
- Terms that are used frequently in reporting ADRs. If a term designates a serious and diagnostically complex ADR it is especially important that the basic requirements for its use in a report are clear. The information on frequency of reporting of a particular ADR is derived from data made available by the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden (now known as the Uppsala Monitoring Centre).

These criteria are interrelated as to their relative importance with respect to various ADRs.

The CIOMS project has proceeded by dealing with ADRs grouped into system-organ classes. As the first step, a group of experts selected terms according to the above criteria. Both the latest version of WHOART and the preliminary version of

MedDRA were consulted. To overcome, at least in part, the problem of differences between these terminologies the project was conducted so that every defined term would also retain validity independent of the ADR terminology used.

The selected terms were submitted for approval by the steering committee. After approval, ADR experts from the pharmaceutical industry were designated to prepare a background paper for each term according to the following layout:

- preamble (generalities, terms of reference, limitations, etc)
- proposed definition of the term (including a list of published definitions)
- basic requirements for validating the reported ADR diagnosis
- additional comments, if any.

The basic requirements to be established refer primarily to terms used in spontaneous reporting, with its shortcomings and frequent lack of detail. So they must be simple enough to suit conditions of spontaneous reporting and be practical rather than exhaustive.

Each group of terms dealt with so far has been discussed at meetings called by CIOMS to review the background papers and produce agreed definitions and basic requirements.

Representatives from the following groups/organisations have been invited to the meetings convened to date:

- the WHO, Division of Drug Management and Policies
- the WHO Collaborating Centre for International Drug Monitoring, Uppsala
- drug regulators (from drug safety units)
- independent experts, mainly from academia and international societies
- authors of background papers, usually from pharmaceutical companies
- members of the steering committee of the project.

Thereafter, a draft report is circulated for comments and approval to:

- authors of the background papers
- independent experts
- the chairman of the meeting.

On receipt of their comments, CIOMS prepares the final version for publication in the journal *Pharmacoepidemiology and Drug Safety*; the first 2 papers were published in the *International Journal of Clinical Pharmacology, Therapy and Toxicology*. Readers' comments are constantly invited but very few have been received so far.

Table I. Proceedings of the Council for International Organization of Medical Sciences (CIOMS) adverse drug reaction (ADR) terminology harmonisation initiative published as of July 1998

Definitions and basic requirements for ADRs involving the liver[12]a
Definitions and basic requirements for ADRs involving drug-induced cytopenia[13]a
Definitions and basic requirements for use of ADR terms: anaphylactic shock, arrhythmia, cardiac failure, hypertension, thrombosis and embolism[14]
Definitions and basic requirements for use of ADR terms: colitis, gastrointestinal haemorrhage, hepatocellular damage, peptic ulcer, pancreatitis[15]
Definitions and basic requirements for use of ADR terms: aplastic anaemia, bone marrow depression, coagulation disorders, agranulocytosis, thrombophlebitis[16]
Definitions and basic requirements for use of ADR terms: dyskinesia, depression, myopathy, neuropathy, paralysis, convulsions[17]
Definitions and basic requirements for use of ADR terms in the system-organ class: vision disorders[18]
Definitions and basic requirements for use of ADR terms in the system-organ classes: myo-, endo-, pericardial and valve disorders[19]
Definitions and basic requirements for use of ADR terms in the system-organ classes: respiratory system disorders and skin disorders[20]
Definitions and basic requirements for use of ADR terms in the system-organ classes: renal and urinary system disorders[21]
Definitions and basic requirements for use of ADR terms in the system-organ classes: central and peripheral nervous systems[22]
Definitions and basic requirements for use of ADR terms in the system-organ class: gastrointestinal system disorders, (remaining terms)[23]
Definitions and basic requirements for use of ADR terms in the system-organ class: cardiovascular system disorders, (remaining terms)[24]

a These first 2 papers were written by CIOMS in cooperation with Roussel-Uclaf, Paris. While the basic objectives of the work of all groups have been the same, certain conceptual differences have still occurred. These first 2 monographs have a somewhat different layout. In addition to the definitions and basic requirements they list criteria for the assessment of causal relationships.

Table II. Phototoxic reaction and photoallergic reaction

Preamble
The terms phototoxic reaction and photoallergic reaction are considered more suitable than photosensitivity toxic reaction and photosensitivity allergic reaction, respectively
All forms of photosensitivity refer to exaggerated or abnormal responses to ultraviolet radiation or to light and most commonly occur on exposed parts of the skin
Photosensitivity reactions may be pleomorphic and include dermatitis-like reactions
Phototoxic reactions, which are nonimmunological events caused by drugs or chemicals, are far more common than photoallergic reactions, which do signify an immunological response
The term phototoxic and photoallergic are specific and should be used with caution in the absence of expert investigation
Definitions
Photosensitivity reaction is an exaggerated 'sunburn' reaction
Phototoxic reactions are exaggerated sunburn-like reactions resulting from the photosensitising substance
Photoallergic reactions are pleomorphic, immunologically-mediated skin reactions
Basic requirements for use of the term
Cutaneous drug reactions satisfying the defined criteria, with special reference to the effects of exposure to light or ultraviolet radiation. Phototoxic reactions occur up to 2 days after exposure and are clearly limited to exposed areas of the skin. Photoallergic reactions occur only after a period of sensitisation, and the skin reaction may extend beyond the exposed areas and may recur with re-exposure to sunlight even without further use of the drug (rechallenge)

The end-product of all the meetings will be published in the form of a cumulative volume and a suitable, user-friendly computer application (CD-ROM) is planned.

3. Results of the Initiative So Far

Up to now, 13 meetings have been held and their proceedings published in 13 papers.[12-24] The areas those papers have covered are listed in table I.

It is not the intention of this article to list all the definitions, but the examples shown in tables II to IV may help the reader to gain an understanding of the objectives and format of the undertaking.

4. Discussion and Conclusions

Use of the definitions and basic requirements established by this CIOMS project is not a compulsory part of any ADR reporting scheme and health professionals are not formally bound to use them. However, they have been drawn up under the auspices of CIOMS and have been agreed upon by medical experts from different countries, representatives of international medical societies, members of national drug surveillance authorities and drug safety units of pharmaceutical companies. They are intended for everyday use by practicing physicians when they fill in ADR reporting forms, and also for use in the validation of reported ADR diagnoses in regulatory and pharmaceutical industry setups. They may also serve educational purposes and thus improve the quality of reporting of ADRs.

In the final publication (in book form and as a CD-ROM) the system-organ class order will be followed so that some related ADR terms, now appearing in different papers because of conceptual changes inevitable in a project of such duration, will be grouped together.

A mechanism for periodic revision and update of the terminology is also planned.

Table III. Pulmonary oedema

Preamble
Pulmonary oedema is part of the pathology of many diseases; it is important, whenever possible, to define and report its cause
Definition
Pulmonary oedema is the extravasation of fluid from the pulmonary capillaries into the interstitial or alveolar spaces of the lung
Basic requirements for use of the term
In some circumstances the diagnosis can be established on clinical grounds alone, such as by the presence of rales of recent origin or appearance of frank oedema fluid in the mouth. In other circumstances radiographic proof is necessary. In the chest x-ray, interstitial pulmonary oedema is characterised by the appearance of septal and perilobular lines/Kerley lines, peribronchial cuffing, subpleural fluid, perihilar haze and diffuse clouding. Alveolaroedema appears as patchy loss of translucency either around the hili or in the lower zones

Table IV. Aortic stenosis

Preamble
Congenital type of aortic stenosis includes valvular, subvalvular (discrete or tunnel type) and supravalvular stenosis. Acquired aortic stenosis can occur as a result of rheumatic endocarditis or fibrotic or calcific degeneration. Bicuspid aortic valve stenosis alone is an important risk factor for development of aortic valve stenosis in middle age. Aortic stenosis alone is always congenital. Rheumatic fever causes mainly aortic regurgitation with some stenosis
Definition
A narrowing of the ventricular outflow tract leading to aorta
Basic requirements for use of the term
Demonstration of the narrowed site, by imaging technique, or of a significant pressure gradient (>20mm Hg) between the left ventricle and the aorta, by either catheterisation or Doppler techniques

Up to now definitions and basic criteria for proper use of some 160 ADR terms have been prepared and published, and it is hoped that about 50 more terms will be defined by the end of 1998. It is considered that with this done, the main work of the Project will have been completed.

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References

1. Venulet J. The WHO Drug Monitoring Programme: the formative years (1968-1975) in drug surveillance: past, present and future. In: Bankowski Z, Dunne JF, editors. Geneva: CIOMS, 1994: 13-21
2. Venulet J. The practicing physician as generator and user of adverse reaction data. Int J Clin Pharmacol Ther Toxicol 1986; 24: 385-9
3. Venulet J, Blattner R, von Bülow J, et al. How good are articles on adverse drug reactions. BMJ 1982; 284: 252-4
4. Venulet J. Informativity of adverse drug reactions data in medical publications. Drug Inf J 1985; 19: 357-65
5. Venulet J. Incomplete information as a limiting factor in causality assessment of adverse drug reactions and its practical consequences. Drug Inf J 1986; 20: 423-31
6. International Reporting of International Adverse Drug Reactions. 1989. Final Report of a CIOMS Working Group I. Geneva: CIOMS, 1990
7. International Reporting of Periodic Drug-Safety Update Summaries. 1992. Final Report of CIOMS Working Group II. Geneva: CIOMS, 1992
8. The Core Safety Date Sheet: standards for good clinical safety labeling practice. 1994. Final Report of CIOMS Working Group III. Geneva: CIOMS, 1995
9. Wood KL. The Medical Dictionary for Drug Regulatory Affairs (MEDDRA). Pharmacoepidemiol Drug Saf 1994; 3: 7-13
10. International Statistical Classification of Disease and Related Health Problems (ICD-10). Geneva: World Health Organization, 1992
11. Bénichou C, Danan G. Réunion de consensus sur les définitions en pharmacovigilance. Thérapie 1987; 42: 347-50
12. Standardization of definitions and criteria of causality assessment of adverse drug reactions: drug-induced liver disorders. Int J Clin Pharmacol Ther Toxicol 1990; 28: 317-22
13. Standardization of definitions and criteria of causality assessment of adverse drug reactions: drug-induced cytopenia. Int J Clin Pharmacol Ther Toxicol 1991; 29: 75-81
14. Basic requirements for the use of terms for reporting adverse drug reactions: anaphylactic shock, arrhythmia, cardiac failure, hypertension, thrombosis and embolism. Pharmacoepidemiol Drug Saf 1992; 1: 39-45
15. Basic requirements for the use of terms for reporting adverse drug reactions: colitis, gastrointestinal haemorrhage, hepatocellular damage, peptic ulcer, pancreatitis. Pharmacoepidemiol Drug Saf 1992; 1: 133-7
16. Basic requirements for the use of terms for reporting adverse drug reactions (III): aplastic anaemia, bone marrow depression, coagulation disorder, thrombophlebitis. Pharmacoepidemiol Drug Saf 1992; 1: 191-6
17. Basic requirements for the use of terms for reporting adverse drug reactions (IV): dyskinesia, depression, myopathy, neuropathy, paralysis, convulsions. Pharmacoepidemiol Drug Saf 1993; 2: 149-53
18. Basic requirements for the use of terms for reporting adverse drug reactions (V): vision abnormal, keratitis, cataract, retinal disorder, acidosis. Pharmacoepidemiol Drug Saf 1993; 2: 189-93
19. Definitions of adverse drug reactions and minimum requirements for their use: cardiovascular disease terms. Pharmacoepidemiol Drug Saf 1993; 2: 591-602
20. Harmonizing the use of adverse drug reaction terms: definitions of terms and minimum requirements for their use: respiratory disorders and skin disorders. Pharmacoepidemiol Drug Saf 1997; 6: 115-27

21. Basic requirements for the use of terms for reporting adverse drug reactions (VIII): renal and urinary system disorders. Pharmacoepidemiol Drug Saf 1997; 6: 203-11
22. Definitions and basic requirements for the use of terms for reporting adverse drug reactions (IX): central and peripheral nervous system terms. Pharmacoepidemiol Drug Saf 1998; 7: 39-49
23. Basic requirements for the use of terms for reporting adverse drug reactions (X): gastrointestinal system disorders. Pharmacoepidemiol Drug Saf. In press
24. Basic requirements for the use of terms for reporting adverse drug reactions (XI): cardiovascular system disorders. Pharmacoepidemiol Drug Saf. In press

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